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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,966	04/20/2005	Carl T Wittwer	P00950-US-01	8958

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Jill T Powlick
Ice Miller
One American Square
Box 82001
Indianapolis, IN 46282-0200

EXAMINER	
CHUNDURU, SURYAPRABHA	
ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
12/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,966	WITTWER ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,17-20,23-30,33-35,37,39-43,45-51,53,55-58,61,65 and 66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,17-20,23-30,33-35,37,39-43,45-51,53,55-58,61,65 and 66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' response to the office action filed on October 07, 2007 has been considered and acknowledged.

Status of Application

2. Claims 2-3, 17-20, 23-30, 33-35, 37, 39-43, 45-51, 53, 55-58, 61, 65-66 are considered for examination in this office action. Claims 1, 4-16, 21-22, 31-32, 36, 38, 44, 52, 54, 59-60, 62-64 are cancelled. Applicants' arguments are fully considered and found persuasive for the reasons that follow.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 49-51, 53, 55-58, 51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claims recite a compound formula, which represents two wave like bonds, which are not clear and indefinite. The meets and bounds of the claims is not clear because it is not clear whether the wave like bonds represent a linker or a hydrogen bond or a spacer. Amendment to clearly recite the said bond would obviate the rejection.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

A. Claims 45-48 are rejected under 35 U.S.C. 102(b) as being anticipated by Wittwer et al. (USPN. 6,174,670).

Wittwer et al. teach a method of claim 45-46, of PCR analysis comprising providing a mixture of a target nucleic acid, PCR reagents, oligonucleotide primers configured for amplifying the target nucleic acid and a dsDNA binding dye, amplifying nucleic acid in the presence of the dye and generating the melting curves from the target nucleic acid, normalizing the melting curve, repeating the providing amplifying normalizing and generating steps with at least one additional target nucleic acid and comparing the normalized melting curves and plotting the fluorescence difference between the normalized curves superimposing a portion of the curve and plotting the fluorescence difference between the curves (see col. 11, line 10-38, col.13, line 26-67, col. 14, line 1-29, col. 15, line 26-45, col. 30, line 30-33, line 61-67, col. 31, line 1-4, Fig. 15, col. 71, line 15-67, col. 17, line 1-46, Fig. 13-26).

With regard to claim 47-48, Wittwer et al. teach that the method comprises the step of plotting the fluorescence difference between normalized curves, and plotting temperature shifted

curves (see col. 70, line 48-67, 71, line 1-14, col. 17, line 1-5, line 29-35, line 47-63). Accordingly Wittwer et al. anticipates the instant claims.

B. Claims 45-48 are rejected under 35 U.S.C. 102(a) as being anticipated by Nurmi et al. (Anal. Biochem., Vol. 299, pp. 211-217, December, 2001).

Nurmi et al. teach a method of claim 45-46, of PCR analysis comprising providing a mixture of a target nucleic acid, PCR reagents, oligonucleotide primers configured for amplifying the target nucleic acid and a dsDNA binding dye, amplifying nucleic acid in the presence of the dye and generating the melting curves from the target nucleic acid, normalizing the melting curve, repeating the providing amplifying normalizing and generating steps with at least one additional target nucleic acid and comparing the normalized melting curves and plotting the fluorescence difference between the normalized curves superimposing a portion of the curve and plotting the fluorescence difference between the curves (page 213, col. 1, paragraph 1, page 214, col. 2, paragraph 1).

With regard to claim 47-48, Nurmi et al. teach that the method comprises the step of plotting the fluorescence difference between normalized curves, and plotting temperature shifted curves (see page 214, col. 2, paragraph 1, page 215, col. 1, line 2-27, col. 2, paragraph 2). Accordingly Nurmi anticipates the instant claims.

C. Claims 17-20, 23-24, 39, 41-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Higuchi et al. (Biotechnology, Vo. 10, pp. 413-417, 1992).

Higuchi et al. teach a PCR reaction analysis of claims 24 comprising mixing a dsDNA binding dye (ethidium bromide) having a saturation of at least 50% with a target nucleic acid, and oligonucleotide primers configured for amplifying the target nucleic acid (see page 414, col.

2, paragraph 1-2 under Results section, Fig 2, page 416, col. 2, paragraph 1-2 under experimental protocol, indicating dye to DNA ratio above 50% saturation); amplifying the target nucleic acid in the presence of the dsDNA binding dye and monitoring the fluorescence of the dsDNA binding dye (page 414, col. 2, paragraph 1-2 under Results section, Fig 2-3, page 416, col. 2, paragraph 1-5 under experimental protocol).

With regard to claim 17, 20, 23, Higuchi et al. teach that the method comprises melting curve analysis and detection of genotype based on the melting curve, target nucleic acid comprises single nucleotide polymorphism and identification of resultant hetero and homoduplexes and mutation scanning on first and second samples and comparing the melting curves (see page 416, col. 2, paragraph 1-5 under experimental protocol, page 415, col.2, Fig. 4-5, page 414, col.2, paragraph 4-5 under Results section).

With regard to claim 18-19, Higuchi et al. teach that the monitoring step is performed using fluorimeter having an excitation range of 450-490nm and an emission detection range of 510-530nm and the dye has an excitation maximum in a range of 410-465nm and an emission maximum is in the range of 450-500nm (see page 416, col. 2, paragraph 4-5 under experimental protocol section).

With regard to claim 39, Higuchi et al. teach that the method comprises closed tube analysis and no reagents are added to the tube subsequent to initiation of amplification (see page 414, col. 2, paragraph 3 under Results section).

With regard to claims 41-42, Higuchi et al. teach monitoring during and after amplification (see page 414, col. 2, paragraph 1-2 under Results section, Fig 2-3, page 416, col. 2, paragraph 1-5 under experimental protocol, page 415, Fig. 4-5). Accordingly Higuchi et al.

anticipates the instant claims.

D. Claims 2-3, 18-19, 23-30, 33-35, 37, 39-43, 45-51, 53, 55-58, 61 are rejected under 35 U.S.C. 102(b) as being anticipated by Sutherland et al. (US 5, 563,037).

Sutherland et al. teach a PCR analysis of claims 24 comprising mixing a dsDNA binding dye having a percent saturation of at least 50% with a DNA sample comprising target nucleic acid and primers configured to amplifying the target nucleic acid, amplifying the target nucleic acid in the presence of the dye and monitoring the fluorescence of the dye (see col. 3, line 40-59, col. 8, line 58-67, col. 9, line 1-28, col. 15, line 4-67).

With regard to claim 2-3, Sutherland et al. teach that the binding dye saturation is of at least 80% or at least 100% (see col. 19-20, table II).

With regard to claim 18-19, Sutherland et al. teach that the monitoring step is performed using fluorimeter having an excitation range of 450-490 nm and an emission detection range of 510-530nm and the dye has an excitation maximum in a range of 410-465nm and an emission maximum is in the range of 450-500 nm (see col. 17, line 38-48).

With regard to claim 23, Sutherland et al. teach that the method comprises mutation scanning on first and second samples and comparing the melting curves (see col. 3, line 40-59, col. 15, line 4-67, col. 9, line 1-28, col. 15, line 4-67).

With regard to claim 45-46, 25-28, 37, 46-48, Sutherland et al. teach that the method comprises normalizing magnitude of melting curve and repeating the normalizing steps with at least one additional target nucleic acid comparing the normalized curves and plotting the fluorescence difference between normalized curves, and temperature shifting of each curve plotting temperature shifted curves (see col. 16, line 20-58, col. 17, line 37-48, Fig.1).

With regard to claim 29-30, Sutherland et al teach that the dyes include YO-PRO-1, BO-PRO-1, TO-PRO-1, TOTO-3, (see col. 14, line 24-25, col. 15, line 5, col. 18, line 43-48, col. 19, table II).

With regard to claim 33-35, Sutherland et al. teach that the method further comprises acceptor labeled probes and a step of monitoring fluorescence from probe, where in the target is no greater than 100 nucleotides (see col.16, line 20-58, col. 17, line 37-48).

With regard to claim 39-43, Sutherland et al. teach that the amplifying and monitoring occur in a closed tube and no reagents are added to the tube subsequent to initiation of amplification and monitoring step comprising melting curve analysis occurs during and post amplification step (see col. 4, line 6-21, col. 8, line 48-57, col. 8, line 58-67, col. 9, line 1-20).

With regard to claim 49-51, 53, 55-58, 61, Sutherland et al. teach that the dsDNA binding dye is a compound having formula as claimed in the claims (see col. 3, line 1-39, col. 40-67, col. line 1-54). Accordingly Sutherland et al. anticipates the instant claims.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 65-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Higuchi et al. (Biotechnology, Vo. 10, pp. 413-417, 1992) in view of Nurmi et al (Anal. Biochem., Vol. 299, pp. 211-217, December, 2001).

Higuchi et al. teach a method of PCR analysis as discussed above in section 4C.

However Higuchi et al. did not teach target nucleic acid as HLA gene.

Nurmi et al. reach a PCR analysis in the presence of a ds binding dye and a probe wherein the method comprises a target nucleic acid comprising HLA gene (see page 213, col. 1, paragraph 1 under all-in-one dry reagent concept, page 215, col. 1, line 2-27, col. 2, paragraph 2).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of monitoring amplification of a target nucleic acid during PCR in the presence of a dsDNA binding dye as taught by Higuchi et al. with a step of including a highly polymorphic HLA gene as a target nucleic acid as taught by Nurmi et al. for the purpose of detecting single nucleotide polymorphisms. One skilled in the art would be motivated to combine the method as disclosed by Higuchi et al. with target HLA gene as taught by Nurmi et al. because Nurmi et al. explicitly taught the real-time monitoring of HLA gene target in the presence of a dsDNA binding dye would eliminate false positives and since

detection of SNPs is very useful in linkage and disease marker association studies, the method provides highthrouput analysis of SNPs (see page 215, col. 1, line 2-27, col. 2, paragraph 2). The ordinary artisan would have had a reasonable expectation of success that inclusion of inclusion of said target would result in a high throughput analysis of highly polymorphic loci such as HLA gene as suggested by Nurmi et al. and such modification of the method would be obvious over the cited prior art.

Response to Arguments

6. With regard to the rejection of claims 2-3, 17-20, 23-28, 30, 33-35, 37, 39-43, 45-48 under 35 USC 102(b) as being anticipated by Wittwer et al., Applicants' arguments and amendment are fully considered and found persuasive in-part and the rejection is withdrawn herein for claims 2-3, 17-20, 23-28, 30, 33-35, 37, 39-43 in view of the persuasive arguments drawn to 50% saturation. However, the rejection is maintained for claims 45-48 and re-written as above since the arguments are found unpersuasive. As discussed in the rejection above Wittwer et al. does teach amplifying, generating and normalizing melting curves by repeating the amplification with a reference nucleic acid and comparing the differences in the melting curves between the reference nucleic acid and the target nucleic acid. Further the arguments based on the use of probes is irrelevant to the instant context, because Wittwer et al. does teach amplification in the presence of a DNA binding dye in addition to the teachings related to the use of probes in amplification. To address these issues, the rejection is re-written as above.

7. With regard to the rejection of claims 29, 49-51, 53, 55-58, 61, 65-66 under 35 USC 103(a) as being obvious over Wittwer et al. in view of Hauglan et al., Applicants' arguments and

amendment are fully considered and found persuasive and the rejection is withdrawn herein in view of the persuasive arguments.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M , Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Suryaprabha Chunduru
Primary Examiner
Art Unit 1637

Prabha Chunduru 12/10/07
SURYAPRABHA CHUNDURU
PRIMARY EXAMINER